

1954-332  
SAS:lew



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of )  
David E. COMINGS )  
Serial No. 09/825,922 ) Examiner: To Be Assigned  
Filed: 5 April 2001 ) Group Art Unit: 1614  
)  
For: METHOD OF PROFILING GENES  
AS RISK FACTORS FOR  
ATTENTION DEFICIT  
HYPERACTIVITY DISORDER

SUBMISSION OF FORMAL DRAWINGS

Assistant Commissioner for Patents  
Washington, D.C. 20231

Dear Sir:

Attached hereto are 11 sheets of formal drawings to replace  
the 10 sheets of informal drawings filed with the subject  
application.

Respectfully submitted,

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Enclosures

Gene	11			12			22			F-ratio	p	Gene score
	N	Mean	SD	N	Mean	SD	N	Mean	SD			
<b>Dopamine genes</b>												
<i>DRD1</i> SNP Ddel												
Lit												
Optimized	39	20.10	10.2	164	17.58	11.1	133	18.30	10.9	0.848	0.43	201
<i>DRD2</i> SNP Taq I A												
Lit												
Optimized	15	15.93	10.3	120	19.50	10.2	201	17.51	11.4	1.560	0.21	020
<i>DRD3</i> SNP MscI												
Lit												
Optimized	152	17.68	11.28	157	18.34	11.0	27	19.16	9.6	0.495	0.63	002
<i>DRD4</i> 48 bp repeat												
Lit												
Optimized	56	19.00	10.9	162	17.98	10.5	118	17.86	11.6	0.223	0.80	002
<i>DRD5</i> 2 dinucleotide repeat												
Lit												
Optimized	74	18.63	11.4	111	19.15	11.3	151	17.38	10.6	0.881	0.41	220
<i>DAT1</i> 3 repeat												
Lit												
Optimized	21	15.33	12.4	142	17.41	10.9	173	19.07	10.8	1.619	0.20	012
<b>Serotonin genes</b>												
<i>HTT4</i> ( <i>SLC6A4</i> ) promoter ins/del												
Lit												
Optimized	85	16.20	10.9	159	19.11	10.9	91	18.28	11.3	1.953	0.14	022
<i>HTR1A</i> SNP C-1918G												
Ind												
Optimized	82	19.00	10.61	177	17.31	11.4	77	19.89	10.1	1.683	0.9	022
												102

**FIG. 1A-1**

Gene	11				12				22				F-ratio	p	Gene score
	N	Mean	SD	N	Mean	SD	N	Mean	SD						
<i>HTR1B</i> ( <i>HTR1DB</i> ) SNP G861C															
Lit															
Optimized	202	18.49	10.9	107	17.30	11.1	27	19.00	11.5	0.496	0.61	002			
<i>HTR1DA</i> SNP T1350C	Ind	266	18.16	11.3	70	19.34	9.7	5	-	-	0.641	0.43	02-	102	
Optimized															
<i>HTR2A</i> SNP T102C MspI	Lit	58	17.88	11.2	172	18.59	11.0	106	17.61	11.0	0.279	0.76	012		
Optimized															
<i>TDO2</i> SNP G->A Int 6BstI	Lit	315	17.98	11.0	17	20.65	10.4	5	-	-	0.951	0.33	02-		
Optimized															
<i>TPH</i> SNP A779 C	Lit	60	19.00	10.4	180	17.73	10.8	96	19.28	11.5	0.705	0.495	002		
Optimized															
Norepinephrine genes															
<i>DBH</i> SNP 7aq	Lit	67	18.81	10.1	168	18.78	11.1	101	16.69	11.3	1.285	0.28	220		
Optimized															
<i>ADRA2A</i> SNP promoter region MspI	Ind	186	17.42	11.1	128	18.8	10.5	22	21.95	11.7	1.96	0.14	012		
Optimized															
<i>ADRA2B</i> del/ins	Ind	155	18.14	11.5	158	18.46	10.6	23	19.73	9.6	0.215	0.81	102		
Optimized															
<i>ADRA2C</i> 6 dinucleotide repeat	Ind	131	18.77	10.5	113	15.79	11.0	92	20.17	11.2	4.45	0.012	202		
Optimized															

**FIG. 1A-2**

Gene	11			12			22			F-ratio	p	Gene score
	N	Mean	SD	N	Mean	SD	N	Mean	SD			
<b>NET (SLC6A2) SNP A1970G MnlI</b>												
Ind												
Optimized	155	17.82	11.2	144	19.04	10.6	38	16.6	11.3	0.914	0.402	120
PNMT SNP G-148A												
Ind												
Optimized	110	16.89	11.1	156	19.59	10.9	66	17.58	10.9	2.05	0.129	012
COMT SNP val 158 met, G1947A, MnlI												
Ind												
Optimized	75	19.42	10.8	175	18.52	11.0	86	16.52	10.8	1.55	0.212	210
ADRA2C:11=<183/<183; 12=het, 22=183/183												

Lit. references for literature-based gene scoring; Ind, gene scoring based on our studies of an independent set of subjects; SNP, single nucleotide polymorphism.

1DRD4: 11=any<4; 12=4/4; 22=any>4.

2DRD5: 11= 148/148; 12=het; 22=non 148/non 148.

3DAT: 11=non 10/non 10; 12= 10/non 10; 22=10/10.

4HTT: 11=SS; 12=SL; 22=LL.

5HTR1DA, TD02 since there were only 2 22s, they were combined with the 12s.

**FIG. 1A-3**

Gene	11			12			22			F-ratio	p	Gene Score			
	% Mean	S.D.	% Mean	S.D.	% Mean	S.D.	% Mean	S.D.	% Mean						
<u>Other Neurotransmitter Genes</u>															
<i>HTR6 SNP (Shinkai et al. 1998)</i>															
ADHD	2.8	12.33	9.7	27.1	18.26	10.3	70.0	18.66	11.2	1.44	.23	012			
ODD		3.0	2.3		3.91	3.1		3.64	3.2	.44	.64	021			
CD		2.11	1.5		3.65	2.6		3.17	2.6	2.05	.13	022			
<i>GABRB3 dinucleotide repeat (Mutirangura et al. 1992)<sup>a</sup></i>															
ADHD	38.0	18.99	10.8	47.9	17.48	11.1	14.1	19.69	10.9	1.05	.35	102			
ODD		3.57	3.1		3.55	3.2		4.47	3.1	1.67	.18	002			
CD		3.01	2.2		2.97	2.4		2.91	2.4	.089	.91	200			
<i>GABBR1 dinucleotide repeat (unpublished)<sup>b</sup></i>															
ADHD	9.5	17.5	11.7	27.0	19.1	11.7	63.5	18.2	10.5	.28	.752	020			
ODD		3.54	3.7		3.66	3.1		3.72	3.1	.047	.953	012			
CD		3.45	2.6		2.72	2.2		3.02	2.4	1.24	.291	201			
<i>CNR1 (Cannabinoid 1 receptor) (Dawson 1995)<sup>c</sup></i>															
ADHD	10.6	19.35	10.9	44.7	18.25	11.0	44.7	18.13	10.9	.174	.83	200			
ODD		4.67	3.1		3.54	3.1		3.56	3.2	1.89	.15	200			
CD		3.09	2.2		2.90	2.3		3.03	2.4	.146	.86	202			
<i>CHRNA4 (Cholinergic, nicotinic, alpha 4) (Weiland, Steinlein 1996)<sup>d</sup></i>															
ADHD	8.0	22.19	9.2	36.2	18.90	10.8	55.8	17.19	11.2	2.35	.096	210			
ODD		5.07	3.0		3.59	3.0		3.55	3.2	2.74	.065	200			
CD		3.11	2.1		2.93	2.3		2.99	2.4	.071	.930	200			

**FIG. 1B-1**

**NMDAR1 (Rupp et al. 1997) Hpa II SNP**

ADHD	44.2	17.31	10.7	45.7	19.31	11.0	10.1	18.56	11.3	1.19	.303	021
ODD		3.79*	3.1		3.79*	3.1		4.84	3.1	2.93	.054	002
CD		2.83	2.3		3.07	2.3		3.28	2.7	.649	.523	012

**ADORA2A (adenosine 2A receptor) (Deckert et al. 1996) C 108 T Rsa I.**

ADHD	33.2	19.95	10.4	44.7	17.57	11.0	22.0	18.97	10.8	1.48	.229	201
ODD		4.04	3.3		3.41	3.1		4.02	3.1	1.52	.219	202
CD		3.39	2.5		2.82	2.1		2.83	2.4	2.04	.131	200

**GRIN2B (glutamate ionotropic, NMDA 2B receptor) T/G (SNP database WIAF-1189).**

ADHD	20.9	17.94	10.6	52.3	19.35	10.6	26.8	18.10	11.1	.582	.559	021
ODD		3.03*	3.0		4.15	3.1		3.50	3.1	3.22	.041	021
CD		2.36*	2.0		3.28	2.4		2.98	2.3	3.59	.029	021

**NOS3 (nitric oxide synthase 3) (Wang et al. 1996)**

ADHD	67.5	18.50	10.9	25.0	18.60	10.6	7.5	17.12	11.6	.186	.830	220	
ODD		3.72	3.1		3.87	3.3		3.29		3.1	.311	.733	120
CD		3.00	2.3		3.12	2.2		2.33		1.9	1.08	.339	120

**Opioids**

**PENK (proenkephalin) (Weber, May 1990; Comings et al. 1999a)e**

ADHD	32.1	18.71	10.4	47.4	18.02	11.3	20.6	18.25	11.0	.053	.948	201
ODD		3.75	3.2		3.75	3.2		3.48	3.1	.255	.775	220
CD		3.03	2.4		3.00	2.4		2.92	2.2	.041	.959	220

**FIG. 1B-2**

*MME* (enkephalinase) (see Methods)<sup>f</sup>.

ADHD	33.9	19.44	11.0	50.9	17.34	10.9	15.2	19.53	10.9	1.26	.284	202
ODD		3.98	3.25		3.44	3.1		3.95	3.0	1.00	.369	202
CD		3.10	2.4		2.81	2.3		3.32	2.4	1.08	.340	202

*ANPEP* (aminopeptidase N) (Watt, Willard 1990) and see Methods, A 257 G

ADHD	27.7	19.25	10.7	51.6	18.37	10.9	20.8	17.60	11.4	.398	.672	210
ODD		3.65	3.1		3.95	3.1		3.30	3.2	.945	.389	120
CD		3.12	2.4		3.05	2.4		2.42	2.0	1.96	.142	210

*NAT1* (N-acetyl transferase) T 1088 A (Dietz et al. 1997; Comings et al. 2000)

ADHD	5.7	21.50	9.5	34.7	19.00	11.2	59.6	17.86	10.8	1.11	.329	210
ODD		4.94	3.7		3.51	3.2		3.68	3.1	1.58	.207	200
CD		4.11	2.8		3.00	2.3		2.88	2.2	2.26	.106	210

## Hormones and neuropeptides

*ESR1* (estrogen 1 receptor) dinucleotide repeat (del Senno et al. 1992; Comings et al. 1999).

ADHD	27.3	19.08	12.0	41.2	17.52	10.6	31.5	18.90	10.3	.673	.511	201
ODD		3.82	3.4		3.56	3.0		3.86	3.0	.293	.746	202
CD		3.26	2.6		2.53*	2.0		3.33	2.5	4.09	.017	202

*CYP19* (aromatase cytochrome P - 450) dinucleotide repeat (Polymeropoulos et al. 1991b)<sup>g</sup>

ADHD	13.4	16.88	11.6	45.2	17.28	11.7	41.4	19.76	9.9	2.11	.122	012
ODD		3.50	3.1		3.33	3.0		4.11	3.3	2.16	.116	102
CD		3.07	2.4		2.52*	2.2		3.37	2.4	4.61	.011	102

FIG. 1B-3

<i>SHBP</i> (sex hormone binding protein)(Xu,Li 1998)													
ADHD	59.8	18.39	11.2	35.2	18.38	10.4	5.0	17.44	11.4	.057	.944	220	
ODD		3.61	3.1		3.76	3.1		3.50	3.1	.108	.897	120	
CD		2.85	2.3		3.11	2.3		3.06	1.8	.465	.628	021	
<i>CRH</i> (corticosteroid releasing hormone) ( <i>Xmn</i> I, Genome Database)													
ADHD	89.8	18.25	11.1	8.6	18.78	8.8	1.5	25.00	7.9	1.189	.285	012	
ODD		3.66	3.2		3.71	2.8		5.60	3.2	.972	.380	012	
CD		2.96	2.4		3.10	2.1		3.80	3.3	.370	.691	012	
<i>OXTR</i> (oxytocin receptor) (Liao et al. 1996) silent C->T in exon 3													
ADHD	47.1	18.48	10.5	44.3	18.0	11.5	8.7	20.11	10.7	.431	.650	102	
ODD		3.59	3.1		3.65	3.2		4.39	2.8	.776	.461	012	
CD		2.77	2.3		3.14	2.3		3.14	2.4	1.06	.347	022	
<i>CCK C-45 T</i> (Ishiguro et al. 1999)													
ADHD	77.0	18.57	10.8	20.4	17.66	11.0	2.2	19.71	14.3	.227	.797	102	
ODD		3.83	3.2		3.30	2.9		3.00	3.0	.909	.404	210	
CD		3.04	2.4		2.71	2.2		3.14	2.3	.555	.574	102	
<i>INS</i> (Hoban,Kelsey 1991; Gade-Andavolu et al. 1999)													
ADHD	58.6	18.04	10.8	36.7	18.47	11.1	4.7	19.46	11.2	.147	.863	012	
ODD		3.68	3.2		3.70	3.1		3.66	3.6	.0014	.998	120	
CD		2.95	2.3		2.98	2.4		3.47	1.6	.334	.716	002	
<i>CD8</i> (Polymeropoulos et al. 1991a) <sup>h</sup>													
ADHD	23.2	17.5	11.3	44.3	18.54	10.9	32.5	18.42	10.9	.122	.885	021	
ODD		3.31	3.2		4.09	3.2		3.44	3.0	1.95	.143	021	
CD		2.53	2.1		3.27	2.5		2.92	2.1	2.44	.088	021	

FIG. 1B-4

*INFG* (Wu,Comings 1998)

ADHD	21.8	18.22	10.9	58.3	18.17	10.9	27.9	18.82	10.8	.109	.896	102
ODD		3.78	2.97		3.69	3.2		3.60	3.2	.068	.934	210
CD		3.11	2.4		3.01	2.4		2.82	2.0	.333	.717	210

*PSI* (Scott et al. 1996)

ADHD	36.0	17.78	11.1	48.0	18.56	10.6	15.2	18.19	11.6	.215	.806	021
ODD		3.44	3.3		3.92	3.1		3.57	3.1	.828	.438	021
CD		2.59	2.1		3.18	2.4		3.30	2.5	2.68	.069	012

\*Significantly lower than highest value by tukey test at  $\alpha = .05$ .

a 11 = <188/<188, 12 = het. 22 = =188/=188

b 11 = =10/=10, 12 = het. 22=>10/>10

c 11 = <5/<5 12=het. 22 = =5/=5

d 11 = =131/=131 12 = het. 22 = >131/>131

e 11 = =178/=178 12 = het. 22 = >178/>178

f 11 = a-c/a-c 12 = het. 22 = d-g/d-g

g 11 = <4/<4 12 = het. 22 = =4/=4

h 11 = 145/145 12 = 145/x 22 = x/x

FIG. 1B-5

Trait	r	r <sup>2</sup>	adjusted r <sup>2</sup>	F	p	# genes
ADHD	.466	.217	.16	3.82	<.0001	22
ODD	.443	.196	.14	3.58	<.0001	20
CD	.451	.203	.15	3.94	<.0001	19

FIG. 2

09825922-070603

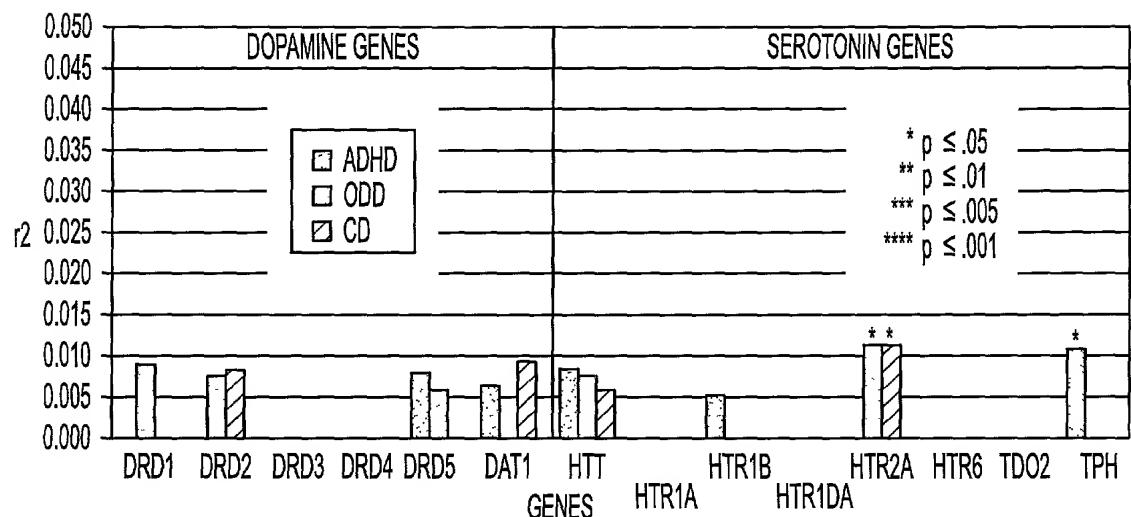


FIG. 3A

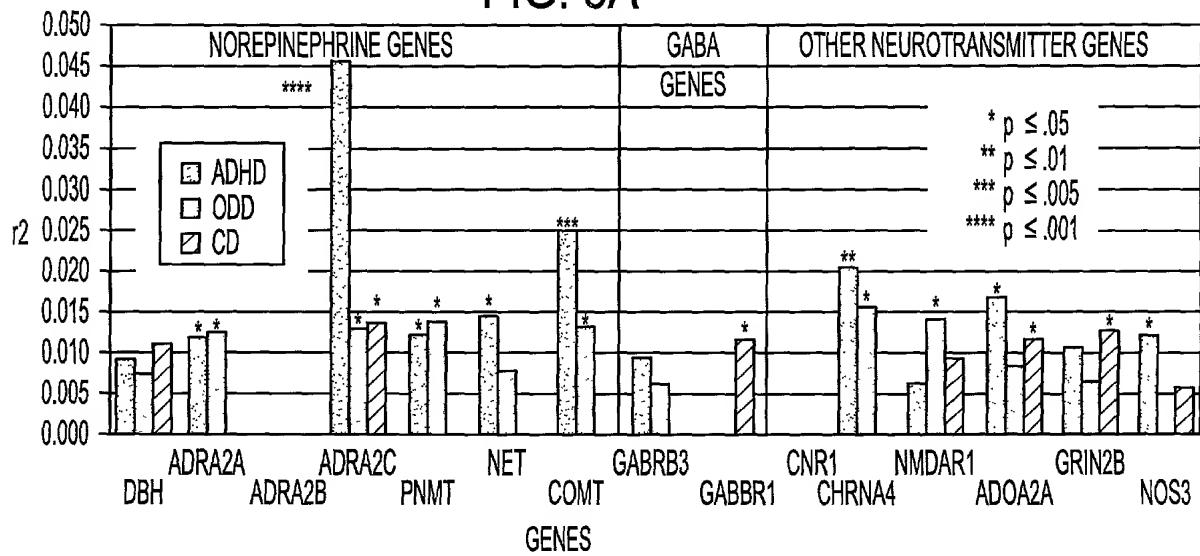


FIG. 3B

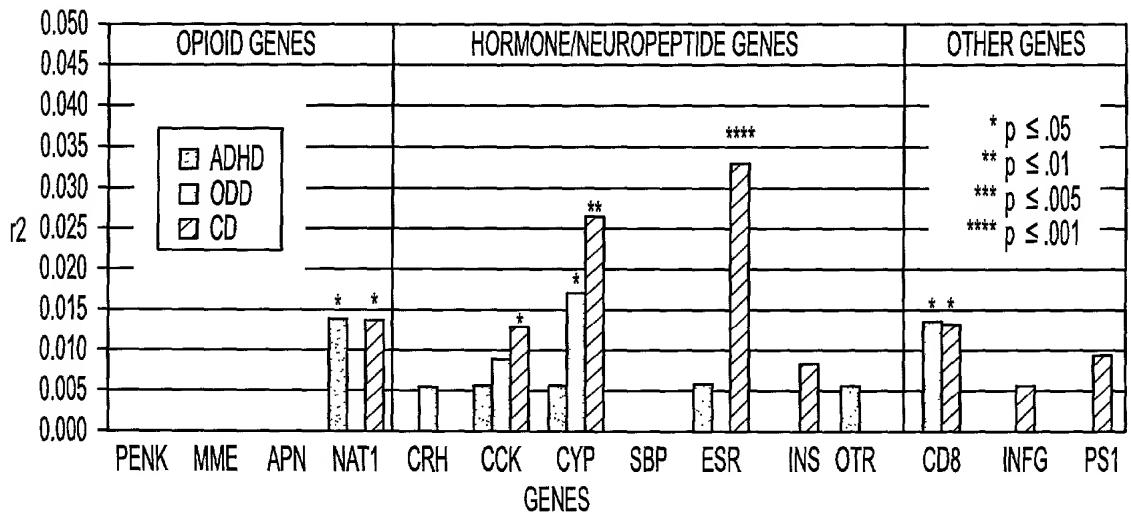


FIG. 3C

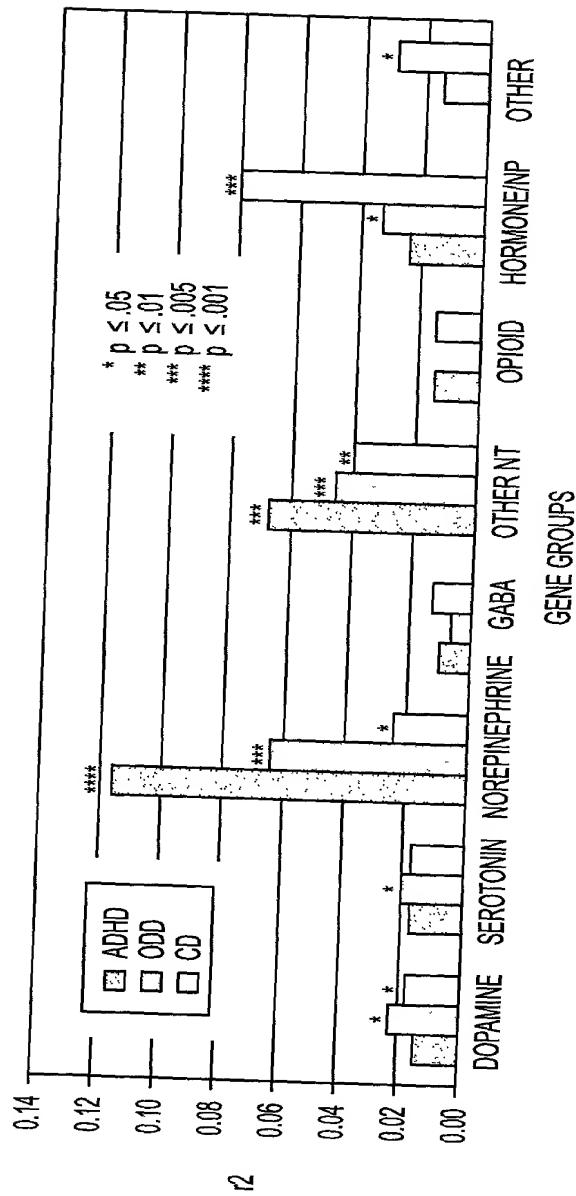


FIG. 4